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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,721	HUSTON ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *9-15,17-19,23-25,27,28 and 30-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8,16,20-22,26 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/1102*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction was received on 2/17/2005. Claims 1-52 are pending in the instant application. Applicant's election with traverse of the invention of species (a) to a gene delivery compound comprising a single chain binding polypeptide and a nucleic acid binding moiety, further defined as binding an erbB2 surface marker, with salmon protamine as the nucleic acid binding moiety, the therapeutic gene to be bound is a tumor suppressor gene, and where the conjugate is C6ML3-9 sFv'-SP in the reply filed on 2/17/2005is acknowledged. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the grounds of restriction for reasons of record as discussed below.

Applicant argues that species (a) is generic to species (a) to (E), that the species are not mutually exclusive and should be rejoined. However, species (a)-(e) each read on a patentably distinct species of gene delivery compounds. Species (b)-(e) differ from species (a) because they each contain an additional effector segment that has a specific function not required by the other species. Therefore, each of the compounds is distinct from each other. Further, searching for species (a) will not result in art relevant to the combination of species (a) and additional effector molecules. The requirement is still deemed proper and is therefore made FINAL.

Claims 9-15,17-19, 23-25, 27, 28, and 30-52 are withdrawn by the examiner from further consideration pursuant to 37 CFR 1.142(b).

Claims 1-8, 16, 20-22, 26 and 29 are currently under examination.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 4 and 5 are drawn to any single chain polypeptide having at least one effector segment which includes at least one cysteinyl residue, where the peptide binds to any surface marker of a mammalian cell. The claims encompass a genus of peptides that would include any ligand or antibody (natural or artificial) that can bind to any surface marker of a mammalian cell.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The claimed genus contemplated in the specification includes any single chain polypeptide having at least one effector segment which includes at least one cysteinyl residue, where the peptide binds to any surface marker of a mammalian cell (Specification pg. 3). This encompasses

any natural, modified or artificial peptide that can bind to a surface marker of a cell. A staggering number of different peptides are encompassed by this genus, given the enormous number of antibody biding epitopes present on surface marker proteins, as well as ligand binding sites.

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the requirement that the peptide bind to the surface marker. The specification only specifically contemplates using C6.5 sFv and C6ML3-9 sFv peptides or variants to bind the erbB2 mammalian cell surface marker. These two peptides cannot bind to any other mammalian cell surface marker with any degree of specificity. Further, the specification fails to identify any structural feature or sequence, common to all single chain polypeptide having at least one effector segment which includes at least one cysteinyl residue that are necessary to bind to any surface marker. The specification does not teach that the peptides have to share any common structural feature, such as a binding site, or amino acid sequence necessary to bind to a marker. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of the single chain polypeptide having at least one effector segment, which includes at least one cysteinyl residue.

The Revised Interim Guidelines state, "when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the

genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for any single chain polypeptide having at least one effector segment which includes at least one cysteinyl residue, where the peptide binds to any surface marker of a mammalian cell. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-8, 16, 20-22, 26 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a gene delivery compound comprising a single chain binding polypeptide and a nucleic acid binding moiety, wherein the compound comprises the C6ML3-9 sFv'SP conjugate, which binds to cells expressing the erbB2 surface marker to deliver a tumor suppressor gene *in vitro*, does not

reasonably provide enablement for a gene delivery compound comprising a single chain binding polypeptide and a nucleic acid binding moiety, wherein the compound comprises the C6ML3-9 sFv'SP conjugate, which binds to cells expressing the erbB2 surface marker to deliver a tumor suppressor gene to any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims encompass a gene delivery compound comprising the C6ML3-9 sFv'-SP conjugate that contains salmon protamine as the nucleic acid binding moiety which binds to a tumor suppressor gene for delivery and where the conjugate binds to any cell that expresses surface marker erbB-2. Wherein the compound's intended use is in a method of delivery to a cell *in vitro*, or gene therapy to introduce a therapeutic gene, such as a tumor suppressor gene into a cell.

The specification does not provide an enabling disclosure for the induction of any therapeutic effect in any cell by using the claimed delivery compound to deliver any tumor suppressor gene. The C6ML3-9 sFv polypeptide is only known in the art to bind to the erbB2 marker (Marks et al. US Patent No. 5,977,322). However, Isola et al. teaches that of 32 human breast carcinomas tested, 9 were negative for erbB2 expression {Isola et al. (1999) Clinical Cancer Research 5: 4140-4145}. Therefore even within a single tumor type there is substantial variation of erbB2 expression. The C6ML3-9sFv polypeptide would be unable to bind to cancer cells that did not express erbB2, and therefore it could not deliver a gene to these cells. Further, all of the working examples described in the specification disclose methods of delivering a reporter gene to erbB2 positive cancer cell lines *in vitro*. The specification does not disclose that the C6ML3-9sFv polypeptide can

be used to deliver a gene to cancer cells *in vivo*, in order to treat cancer. Demonstrating that C6ML3-9 sFv polypeptide can successfully deliver a gene to a cell expressing erbB2 for expression of a reporter gene *in vitro*, does not provide sufficient evidence that the C6ML3-9 sFv polypeptide can be used for gene therapy, to deliver any tumor suppressor gene to any cell for expression *in vivo*.

Further, the claims encompass any tumor suppressor gene. However, the specification does not provide guidance on the specific tumor suppressor genes, promoters, or plasmids to be used, or the tumor cells to be treated with the compound. Verma et al. states that in general, the Achilles heel of gene therapy is gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2}. Marshall concurs, stating that, difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field, and that, many problems must be solved before gene therapy will be useful for more than the rare application {Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1}. Orkin et al. further states in a report to the NIH that, none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated, and that, while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol {Orkin et al. (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2}. Among the many factors that the art teaches affect efficient gene delivery and sustained gene

expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the latter issue, Verma states that, the search for such combinations is a case of trail and error for a given cell type {Verma, (1997) Nature, 389, page 240}. Thus, given the total lack of guidance in the specification on how to produce any therapeutic effect with any tumor suppressor gene in any cell, *in vivo*, using the C6ML3-9 sFv'-SP conjugate, the lack of guidance in the specification on how to use the C6ML3-9 sFv'-SP conjugate to a gene to any cell that does not express the erbB2 surface marker, and the teachings in the art that gene therapy remains highly unpredictable, a skilled artisan would be unable to practice the invention, except as a gene delivery compound comprising a single chain binding polypeptide and a nucleic acid binding moiety, wherein the compound comprises the C6ML3-9 sFv'SP conjugate, which binds to cells expressing the erbB2 surface marker to deliver a tumor suppressor gene *in vitro,* without undue and extensive experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22is vague because it reads on inhibiting a "DNA encoding a therapeutic gene." DNA does not encode genes it encodes proteins. Therefore the metes and bounds

of the claims invention cannot be determined. Claim 26 depends on claim 22.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Wagner et al. {Wagner et al. (1990) Proc. Natl. Acad. Sci. USA 87:3410-3414}.

Claims 1,3 and 4 encompass a gene delivery compound comprising any single chain binding polypeptide having at least one cysteinyl residue and a nucleic acid binding moiety. Wherein the nucleic acid is associated reversibly with said moiety and the polypeptide binds to any surface marker of a mammalian cell.

Wagner et al. provides guidance on the development of a nucleic acid delivery system that uses receptor-mediated endocytosis to carry DNA molecules into cells (Abstract). Wagner et al. teaches a compound for use in the delivery system, comprising a transferrin peptide covalently linked to salmon protamine with a heterobifunctional cross linking agent, such as succinimidyl 3-(2-pyridyldithio) propionate (Materials and Methods pg. 3410-3411). Wagner et al. teaches that all metabolically active cells take up transferring-iron complexes (pg. 3410, col. 1). Thus, the compound taught by Wagner et al. can be used to target any cell. Finally, Wagner et al. teaches that the compound can be used to deliver any gene, such as the luciferase gene to eukaryotic cells (pg. 3410, col. 1; pg. 3413, col.1). Thus, by teaching all the limitations of the claims as written, Wagner et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 16, 20-22, 26 and 29 rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. {Wagner et al. (1990) Proc. Natl. Acad. Sci. USA 87:3410-3414}, further in view of US Patent No. 5,977,322, hereafter referred to as Marks et al. and of International Patent Application No. WO 00/04922, hereafter referred to as Konadu et al.

The claims encompass a gene delivery compound comprising the C6ML3-9 sFv'-SP conjugate that contains salmon protamine as the nucleic acid binding moiety which binds to a tumor suppressor gene for delivery and where the conjugate binds to the cell surface marker erbB-2.

Wagner et al. provides guidance on the development of a nucleic acid delivery system that uses receptor-mediated endocytosis to carry DNA molecules into cells (Abstract). Wagner et al. teaches a compound for use in the delivery system, comprising a transferrin peptide covalently linked to salmon protamine with a heterobifunctional cross linking agent, such as succinimidyl 3-(2-pyridyldithio) propionate (Materials and Methods pg. 3410-3411). Wagner et al. teaches that all metabolically active cells take up

transferring-iron complexes (pg. 3410, col. 1). Thus, the compound taught by Wagner et al. can be used to target any cell. Finally, Wagner et al. teaches that the compound can be used to deliver any gene, such as the luciferase gene to eukaryotic cells (pg. 3410, col. 1; pg. 3413, col.1). Wagner et al. does not teach that the gene to be delivered is a tumor suppressor gene, that SMCC or sulfoSMCC is the heterobifunctional cross linking agent, that the compound comprises a spacer sequence, that the peptide is C6ML3-9 sFv, or that the cell surface marker to be bound is erbB-2.

Marks et al. supplements the teachings of Wagner et al. by providing guidance on the use of the C6ML3-9 sFv polypeptide to deliver therapeutic effector molecules to cells over expressing erbB-2 (Abstract; pgph 67, pgph 76). Where the therapeutic molecule could be a radionuclide. Marks et al. teaches that C6 sFv antibodies specifically bind to the erbB-2 marker, which is expressed on many cancers (col. 2, lines 1-5). Therefore, the C6ML3-9 sFv can be used to specifically bind to tumor cells that express erbB-2. Thus the protein delivery compound taught by Marks et al. can be used to specifically deliver molecules to specific cells. Finally, Marks et al teaches that the C6ML3-9 sFv protein may be directly joined to the effector molecule, or that the molecules may be separated by a peptide spacer consisting of one or more amino acids (pgph 123). Generally the spacer will have no specific biological activity other than to join the proteins or to preserve some minimum distance or other spatial relationship between them. However, the constituent amino acids of the spacer may be selected to influence some property of the molecule such as the folding, net charge, or hydrophobicity (pgph 123).

Konadu et al. supplements the teachings of Wagner et al. by providing guidance on the use of SMCC as a heterobifunctional cross-linking agent to covalently bind to a protein to a carrier (pg. 11 pgph 2).

It would have been *prima facie* obvious at the time of the claimed invention to modify the teachings of Wagner et al. by linking the salmon protamine to the C6ML3-9 sFv taught by Marks et al. using any heterobifunctional cross linking agent, such as the SMCC taught by Konadu et al. in order to transfect a tumor cell expressing erbB-2 with a tumor suppressor gene.

One of ordinary skill in the art would have been motivated by the teachings of Marks et al. that C6ML3-9 sFv can be used to specifically bind to tumor cells, to modify the C6ML3-9 sFv by cross linking it with salmon protamine taught by Wagner et al. in order to deliver a therapeutic tumor suppressor gene sequence to the specifically to the tumor cells in order to treat cancers that express erbB-2. The gene delivery compound containing the salmon protamine taught by Wagner can be used to deliver any nucleic acid sequence, including any tumor suppressor gene. It would be obvious to the skilled artisan to use any heterobifunctional cross linking agent, such as the SMCC taught by Konadu et al., to crosslink the salmon protamine to the C6ML3-9 sFv.

The person of ordinary skill in the art would have had a reasonable chance of success because cross linking a protein such as C6ML3-9 sFv to carrier such as salmon protamine using a heterobifunctional cross linking agent is a routine technique in the art and would comprise a minor modification prior to the gene delivery system taught by Wagner et al.

Applicant should note that intended use is not given patentable weight in claims

that define a structure with functional language that reads solely on intended use. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). It is noted that the use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand-alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto, 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent

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